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Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress

RONG ZHANG, JULIE H. ZUCKERMAN,
JAMES A. PAWELCZYK, AND BENJAMIN D. LEVINE
Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas,
and University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75231

Zhang, Rong, Julie H. Zuckerman, James A. Pawelczyk, and Benjamin D. Levine. Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress. *J. Appl. Physiol.* 83(6): 2139–2145, 1997.—Our aim was to determine whether the adaptation to simulated microgravity (µG) impairs regulation of cerebral blood flow (CBF) during orthostatic stress and contributes to orthostatic intolerance. Twelve healthy subjects (aged 24 ± 5 yr) underwent 2 wk of −6° head-down-tilt (HDT) bed rest to simulate hemodynamic changes that occur when humans are exposed to µG. CBF velocity in the middle cerebral artery (transcranial Doppler), blood pressure, cardiac output (acetylene rebreathing), and forearm blood flow were measured at each level of a ramped protocol of lower body negative pressure (LBNP; −15, −30, and −40 mmHg × 5 min, −50 mmHg × 3 min, then −10 mmHg every 3 min to presyncope) before and after bed rest. Orthostatic tolerance was assessed by using the cumulative stress index (CSI; mmHg × minutes) for the LBNP protocol. After bed rest, each individual's orthostatic tolerance was reduced, with the group CSI decreased by 24% associated with greater decreases in cardiac output and greater increases in systemic vascular resistance at each level of LBNP. Before bed rest, mean CBF velocity decreased by 14, 10, and 45% at −40 mmHg, −50 mmHg, and maximal LBNP, respectively. After bed rest, mean velocity decreased by 16% at −30 mmHg and by 21, 35, and 39% at −40 mmHg, −50 mmHg, and maximal LBNP, respectively. Compared with pre-bed rest, post-bed-rest mean velocity was less by 11, 10, and 21% at −30, −40, and −50 mmHg, respectively. However, there was no significant difference at maximal LBNP. We conclude that cerebral autoregulation during orthostatic stress is impaired by adaptation to simulated µG as evidenced by an earlier and greater fall in CBF velocity during LBNP. We speculate that impairment of cerebral autoregulation may contribute to the reduced orthostatic tolerance after bed rest.

microgravity; blood flow; orthostasis; Doppler

ALTHOUGH ORTHOSTATIC INTOLERANCE is a frequent consequence of the cardiovascular adaptation to microgravity or ground-based simulations such as bed-rest deconditioning, the underlying mechanisms remain unclear (7, 18, 30). Most hypotheses focus on blood pressure regulation and include deconditioning-related hypovolemia (30); changes in cardiovascular mechanics (19, 21); compromised ability to increase total peripheral resistance (7); and impairment of baroreflex regulation of heart rate (9, 11). However, syncope during orthostatic stress ultimately occurs because of a reduction in cerebral blood flow (CBF) sufficient to cause loss of consciousness.

There are two mechanisms by which this process may occur. The first and most commonly accepted hypothesis is that the fall in CBF is secondary to systemic hemodynamic collapse (4). Alternatively, we and others have suggested that there may be a cerebral vasoconstriction associated with a primary impairment of cerebral autoregulation that may compromise CBF during orthostatic stress (6, 14, 19). Contrary to what might be predicted from the traditional concept of cerebral autoregulation, we observed a decrease in mean CBF velocity during graded lower body negative pressure (LBNP) despite maintenance of mean arterial pressure. Furthermore, in subjects who were prone to syncope during LBNP, decreases in CBF velocity occurred earlier at lower levels of LBNP than in those subjects who regulated arterial pressure more successfully. These results suggested that impairment of cerebral autoregulation may contribute to orthostatic intolerance (19).

Prolonged head-down-tilt (HDT) bed rest has been used to simulate hemodynamic changes that occur when humans are exposed to microgravity and often results in orthostatic intolerance (5, 7). We conducted the present study to determine the effects of simulated microgravity on cerebral hemodynamics during orthostatic stress. We hypothesized that a decrease in CBF velocity would be observed at lower levels of LBNP after bed rest, associated with a reduction in orthostatic tolerance. Furthermore, we speculated that these changes also would be associated with an increase in the correlation between variations in arterial pressure and CBF velocity, indicating an increased dependence of flow velocity on changes in pressure and impairment of cerebral autoregulation.

METHODS

Subjects. Twelve healthy subjects (11 men and 1 woman) with a mean age of 24 ± 5 yr, height of 185 ± 23 cm, and weight of 79 ± 3 kg were studied. No subject used recreational drugs or tobacco products or had chronic medical problems. No subject was an endurance-trained athlete, and subjects were excluded if they exercised for >30 min/day more than three times a week, using either dynamic or static exercise. Subjects were screened by using medical history and a physical examination, electrocardiogram, and echocardiogram. All subjects signed an informed consent document approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Microgravity simulation. After an initial series of baseline experiments, head-to-foot gravitational gradients were reduced by placing the subjects at complete bed rest, with −6° HDT. Subjects were allowed to raise up on one elbow for meals but otherwise were restricted to the head-down position at all times. Subjects were housed in the General Clinical Research Center at the University of Texas Southwestern

Medical Center and given a standard diet consisting of 2,827 ± 609 cal/day, including 5.2 ± 1.2 gm/day of sodium. Fluids were allowed ad libitum, but all fluid intake and urine output were carefully recorded. All experiments were repeated after 18 days of HDT.

Orthostatic stress. Progressive LBNP was used to decrease central blood volume in a graded fashion and facilitate physiological evaluation during orthostatic stress. Subjects were placed in a Plexiglas LBNP box that was sealed at the level of the iliac crests. Suction was provided by a vacuum pump and controlled with a variable autotransformer. Pressure differential between the chamber and atmosphere was measured with a mercury manometer. After at least a 30-min baseline period of quiet rest, the magnitude of the suction was increased in a stepwise fashion according to the following protocol: −15 mmHg × 5 min, −30 mmHg × 5 min, −40 mmHg × 5 min, −50 mmHg × 3 min, and increasing negative pressure increments by −10 mmHg every 3 min to the point of maximal tolerance. LBNP was discontinued if the subject developed signs and/or symptoms of presyncope: sudden onset of nausea, sweating, light headedness, bradycardia, or hypotension (sustained systolic blood pressure <80 mmHg). Orthostatic tolerance was assessed by using the cumulative stress index, calculated as the sum of the products of the duration of LBNP and the magnitude of the negative pressure at each level (mmHg × minutes).

Data acquisition. All experiments were performed in the morning, at least 2 h after a light breakfast, and >12 h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory, with an ambient temperature of 22 ± 1°C. Heart rate was continuously monitored by electrocardiography (Hewlett-Packard), and beat-to-beat blood pressure was measured in the finger by photoplethysmography (Finapres, Ohmeda). Intermittent blood pressure was measured in the arm by electrosphygmomanometry (Suntech) with a microphone placed over the brachial artery and the Korotkoff sounds gated to the electrocardiograph.

Cardiac output was measured with a standard foreign gas rebreathing technique by using acetylene as the soluble and helium as the insoluble gas. Adequate mixing of the rebreathing gas in the lung was confirmed by a constant level of helium in all cases. This technique has been described previously and has been validated against both indocyanine dye and thermodilution methods in healthy subjects and in patients with significant cardiopulmonary disease (16, 27, 29). Cardiac output was measured at baseline and at each level of LBNP up to −40 mmHg, then measured at every other level of LBNP to allow at least 5 min for the inhaled acetylene to be cleared after the previous measurement. Mean arterial pressure obtained during the rebreathing was divided by cardiac output to calculate systemic vascular resistance.

Forearm blood flow was measured by using venous occlusion plethysmography. A mercury-in-Silastic strain gauge was placed over the largest part of the subject's forearm. Occlusion cuffs were placed at the wrist and upper arm. After inflation of the distal cuff to exclude hand blood flow, three to five flow measurements were made over a 1- to 2-min period at a proximal cuff pressure of 40 mmHg. Blood flow was estimated from the rate of increase on forearm volume during venous occlusion. These measurements were then averaged and divided by mean blood pressure (Suntech), recorded simultaneously with flow, to calculate forearm vascular resistance at rest and at each level of LBNP.

For measurements in the brain, we used transcranial Doppler to measure blood flow velocity in the middle cerebral artery (MCA) (1). This technique allows noninvasive and repeatable measurements of blood flow velocity on a beat-to-

beat basis. A 2-MHz probe (Pioneer, Nicolet) was placed over the temporal window and fixed at a constant angle and position to obtain signals from the MCA according to standard techniques (2). The reproducibility of velocity measurements during LBNP was assessed in a separate group of four healthy subjects (aged 33 ± 7 yr) at time intervals ranging from 2 mo to 1 yr. No significant change in percent decreases of velocity (measurements of velocity at each level of LBNP divided by baseline value) during maximal LBNP was observed between the repeated tests, confirming the reproducibility of this response.

The finger pressure and MCA-velocity signals were sampled at 1 kHz and digitized at 12 bits (Metrabyte, DAS-20) with use of a personal computer. Real-time beat-to-beat mean values of pressure and velocity were generated and displayed by using custom data-acquisition software. Mean pressure and velocity averaged over the last minute of each level of LBNP were considered as steady-state values for statistical comparison. For the last six subjects studied, continuous beat-to-beat mean velocity was obtained during a 6-min control period and for 3 min at each level of LBNP and recorded along with beat-to-beat mean pressure for off-line coherence analysis. This capability was not available during the experiments in the first six subjects, and therefore the data are only available for $n = 6$.

Gosling pulsatility (systolic − diastolic/mean velocity) was used as an index of vascular resistance. This ratio describes the shape of the CBF velocity waveforms. It represents the proportion of flow energy that is pulsatile and is related to the elasticity of the vascular system; changes in pulsatility reflect changes in cerebral small-vessel resistance (31). Because pulsatility of the velocity waveform is affected importantly by systemic pulse pressure, we corrected for this effect by dividing the velocity pulsatility by arterial pressure pulsatility to derive a corrected pulsatility ratio (19).

Coherence analysis. The correlation between the beat-to-beat changes in arterial pressure and CBF velocity was evaluated by the magnitude-squared coherence function (MSC), defined as

$$\text{MSC}(f) = \frac{|\text{S}_{xy}(f)|^2}{\text{S}_{xx}(f)\text{S}_{yy}(f)}, \quad 0 \leq \text{MSC}(f) \leq 1,$$

$$\text{for} \quad \text{S}_{xx}(f)\,\text{S}_{yy}(f) \neq 0$$

where $\text{S}_{xx}(f)$ and $\text{S}_{yy}(f)$ are the autopower spectra of signals $x(t)$ and $y(t)$, and $\text{S}_{xy}(f)$ is the cross-power spectrum between $x(t)$ and $y(t)$. A coherence of one at a given frequency indicates perfect correlation between the two variables, whereas a coherence of zero indicates no correlation (22).

In this study, coherence estimation was based on the Welch method (8). Beat-to-beat values of mean pressure and velocity were linearly interpolated and resampled at 1 Hz to provide an equal-spaced time series for spectral analysis. A low-frequency coherence index defined as the spectral area of MSC(f) between 0.05∼0.15 Hz and a high-frequency coherence index defined as the spectral area of MSC(f) between 0.15∼0.35 Hz were calculated for statistical analysis. The determination of the frequency intervals was based on the results of spectral analysis of arterial pressure variability, which showed 0.10-Hz low-frequency and 0.25-Hz high-frequency components (25), and a consideration that cerebral autoregulation would respond to changes in arterial pressure within several seconds (26). Data analysis was performed with commercially available software (DADiSP, DSP Development, Cambridge, MA).

Statistical analysis. Changes in hemodynamic variables and coherence index at each level of LBNP were compared by using one-way analysis of variance with Duncan's post hoc

Table 1. *Cardiovascular response to lower body negative pressure*

	Mean Arterial Pressure, mmHg		Heart Rate, beats/min		Stroke Volume, ml		Cardiac Output, l/min		Systemic Vascular Resistance, dyn·s·cm⁻⁶		Forearm Blood Flow, ml·min⁻¹·100 ml⁻¹		Forearm Vascular Resistance, mmHg· ml⁻¹·min·100 ml	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Baseline, mmHg	85 ±2	87 ±2	71 ±3	84† ±3	90.0 ±5.4	68.0† ±3.2	6.28 ±0.25	5.63† ±0.23	1,093 ±48	1,248† ±46	3.40 ±0.20	3.13 ±0.29	27.8 ±2.0	32.4 ±3.5
−15	86 ±3	86 ±3	76 ±3	94*† ±3	72.7* ±5.0	48.6*† ±2.4	5.44* ±0.32	4.49† ±0.16	1,310* ±83	1,570*† ±42	3.07 ±0.50	2.57* ±0.25	36.2* ±2.1	39.7 ±4.5
−30	80 ±2	84 ±2	87* ±4	110*† ±5	50.7* ±4.4	35.8*† ±2.5	4.25* ±0.24	3.82* ±0.20	1,536* ±75	1,770*† ±64	2.84 ±0.48	2.11* ±0.17	40.8* ±3.3	44.7 ±4.2
−40	81 ±3	81 ±4	97* ±4	120*† ±5	39.4* ±2.9	30.5*† ±1.9	3.70* ±0.19	3.63* ±0.20	1,777* ±64	1,817* ±88	2.49* ±0.38	1.92* ±0.19	44.3* ±3.2	50.4* ±7.6
−60	80 ±3	73* ±4	116* ±7	150*† ±6	31.5* ±4.0	17.8*† ±2.1	3.37* ±0.30	2.67*† ±0.27	1,934* ±136	2,313*† ±136	2.26* ±0.26	1.98* ±0.53	47.2* ±3.1	55.4* ±15.3

Values are means ± SE; n = 12 subjects. Pre, before bed rest; post, after bed rest. * $P < 0.05$ compared with baseline. † $P < 0.05$ compared with pre-bed rest.

tests for multiple comparisons. Changes in hemodynamic variables and coherence indexes before and after bed rest were compared by using a paired t-test. Statistics were performed by using a PC-based software program (WinSTAR, AndersonBell).

RESULTS

Orthostatic tolerance. After 2 wk of bed rest, each individual's orthostatic tolerance was reduced and the group cumulative stress index decreased by 24% from 954 ± 372 to 732 ± 241 (SD) mmHg × minutes ($P <$ 0.02). These data are specific to this LBNP protocol and may not be comparable to cumulative stress values derived by using other protocols. Similar to the reduction in the cumulative stress index, the group maximal LBNP level decreased from 72 ± 15 to 61 ± 12 mmHg ($P < 0.01$). Seven of twelve subjects had a reduction in maximal LBNP level ranging from 10 to 30 mmHg. The other five subjects achieved the same maximal LBNP

level before and after bed rest, but with a reduction in the duration of LBNP at the highest level. Steady-state values for hemodynamic variables during LBNP are reported in Table 1.

Arterial pressure and CBF velocity. Representative waveforms of arterial pressure and CBF velocity from one subject at rest and during LBNP are shown in Fig. 1, with mean group data shown in Fig. 2. Before bed rest, mean arterial pressure did not change significantly from rest to −50 mmHg LBNP (Fig. 2A). At maximal LBNP, it fell significantly at the point of presyncope. In contrast, mean CBF velocity decreased significantly by 14, 20, and 45% at −40 mmHg, −50 mmHg, and maximal LBNP ($P < 0.05$), respectively (Fig. 2B). Simultaneously, the corrected pulsatility ratio increased significantly at −40 mmHg and maximal LBNP ($P < 0.05$), suggestive of downstream cerebral vasoconstriction (Fig. 2C).
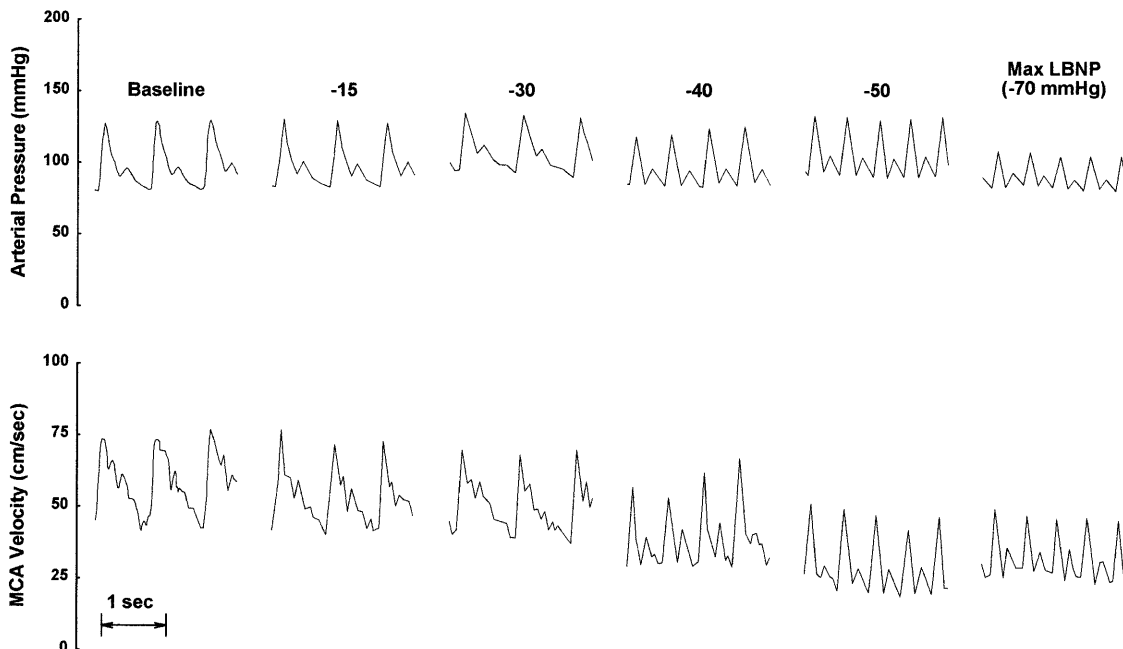

Fig. 1. Representative waveforms of arterial pressure and cerebral blood velocity from 1 subject at rest and during progressive lower body negative pressure (LBNP). Velocity waveforms are generated by computer and acquired simultaneously with pressure waveform. MCA, middle cerebral artery; Max, maximal.
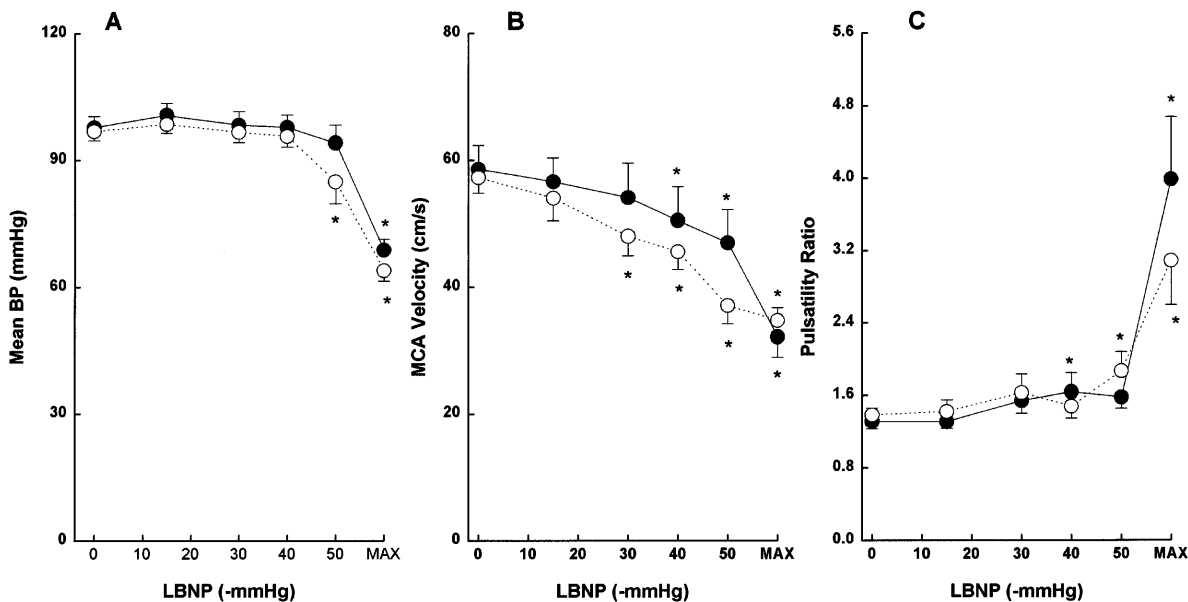
Fig. 2. Time course of changes in mean arterial blood pressure (BP; *A*), cerebral blood flow velocity measured in MCA (*B*), and pulsatility ratio during progressive LBNP (*C*). Values are means ± SE. Pre-bed-rest maximal (max) LBNP, 72 ± 15 mmHg; post-bed-rest max LBNP, 61 ± 12 mmHg. ●, Pre-bed rest; ○, post-bed rest. *$P < 0.05$ compared with rest.

After bed rest, mean arterial pressure decreased significantly at −50 mmHg and maximal LBNP ($P < 0.05$) (Fig. 2*A*). Mean CBF velocity fell at lower levels of LBNP compared with pre-bed rest, with significant decreases from baseline by 16% at −30 mmHg and 21, 35, and 39% at −40 mmHg, −50 mmHg, and maximal LBNP, respectively ($P < 0.05$) (Fig. 2*B*). Similar to pre-bed rest, the corrected pulsatility ratio increased significantly at −50 mmHg and maximum LBNP ($P < 0.05$) (Fig. 2*C*). Compared with pre-bed rest, there was no significant change between the baseline velocity measurements. However, mean velocity was less by 11, 10, and 21% at −30 mmHg, −40 mmHg, and −50 mmHg LBNP, respectively, after compared with before bed rest ($P < 0.05$).

Coherence analysis. Representative time series (Fig. 3, *A* and *C*) and power spectra (Fig. 3, *B* and *D*) of beat-to-beat changes in mean arterial pressure and CBF velocity from one subject at rest are shown in Fig. 3. Similar to the changes in arterial pressure, variation of velocity showed a range of 29% change around the mean value and a complex pattern with prominent low-frequency components (Fig. 3, *C* and *D*). Typical coherence functions estimated from the beat-to-beat changes in pressure and velocity are shown in Fig. 4 at rest and during LBNP. There was an obvious peak in the low-frequency band (0.05∼0.15 Hz) at rest, and the low-frequency coherence indexes increased during LBNP with the peak value approaching one at −40 and −50 mmHg LBNP, suggesting that cerebral autoregulation in the low-frequency range was impaired during high-level LBNP. There was no significant change in the high-frequency coherence index during LNBP. After bed rest, there was a trend for an increase in the low-frequency coherence index at baseline, with a similar augmentation during LBNP as observed before bed rest

(Figs. 4 and 5). For all subjects, the low-frequency coherence index increased by 61 and 66% at −40 and −50 mmHg LBNP before bed rest, respectively ($P < 0.05$) (Fig. 5). After bed rest, the low-frequency coherence index increased earlier by 33% at −30 mmHg LBNP ($P < 0.05$) (Fig. 5) and 45 and 50% at −40 and −50 mmHg LBNP, respectively (Fig. 5). However, because of subject dropout at higher levels of LBNP after bed rest, the increase in the low-frequency coherence index could not be demonstrated statistically at high levels of LBNP.

DISCUSSION

The primary new finding of the present study is that mean CBF velocity decreased earlier at lower levels of LBNP in the absence of changes in arterial pressure, and the magnitude of the decrease was greater after 2 wk of head-down-tilt bed rest, associated with a substantial reduction in orthostatic tolerance. Furthermore, the coherence between changes in pressure and velocity increased significantly during LBNP, and these increases occurred at lower levels of LBNP after bed rest. These results suggest an impairment of cerebral autoregulation after bed rest and may contribute to the reduced orthostatic tolerance.

Methodological considerations. In the present study, we used transcranial Doppler to measure flow velocity in the MCA to estimate changes in CBF (1, 2). It is important to emphasize that velocity is not necessarily equal to flow. Changes in velocity are proportional to changes in flow only if the diameter of the MCA is maintained constant (19). Because of the anatomic location of the MCA and technical limitations, measurement of MCA diameter in humans may be difficult. Despite this difficulty, both angiographic studies (15)
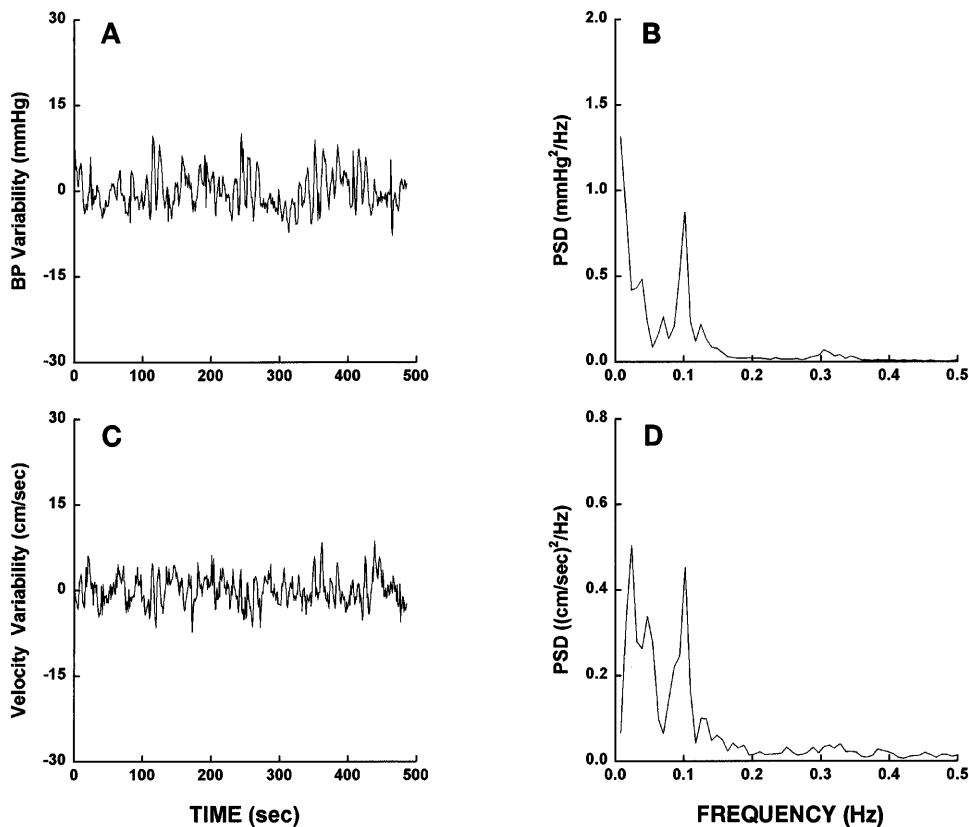
Fig. 3. Representative time series and power spectra of beat-to-beat variability of mean arterial pressure and cerebral blood flow velocity from 1 subject at rest. *A*: time series of mean arterial BP. *B*: spectrum of *A*; *C*: time series of mean cerebral blood flow velocity; *D*: spectrum of *C*. PSD, pulsed Doppler.

and direct visualization of the MCA during surgery (13) have suggested that, during a variety of stimuli known to affect CBF, the diameter of the MCA changes minimally (<3.0%). Thus it is likely that changes in velocity measured by Doppler are proportional to changes in flow (19).

To investigate the dynamic properties of cerebral autoregulation, we took the advantage of coherence analysis to quantify the dependence of changes in velocity on the changes in arterial pressure (12). Coherence analysis is a frequency-domain measurement of correlation between two signals (22). Therefore, a high coherence suggests a high correlation between the changes in velocity and pressure and may represent ineffective autoregulation (12). Alternatively, a low coherence suggests a poor correlation between changes in velocity and pressure and may represent effective autoregulation. However, coherence estimation may be degraded by extraneous noise presented in the measurements (22). In the present study, the estimation was based on beat-to-beat changes in mean arterial pressure and velocity, and the random measurement noise was therefore likely to be reduced by this averaging process. Moreover, the high coherence values estimated during LBNP suggest that the noise level in such recordings was relatively low.

In the present study we assumed that relative changes in cerebral perfusion pressure would be reflected by the relative changes in mean arterial pressure in subjects in the supine position. We measured arterial pressure in the finger by using the method of photoplethysmography. The reliability of this method for arterial pressure

measurement has been proved in both the time and frequency domain (24). Considering that the arterial pressure wave moves at a velocity of ~5–8 m/s in large vessels (23), we find that the time delay between the finger arterial pressure and cerebral arterial pressure should be small and negligible. Furthermore, although waveforms of arterial pressure differ in different vascular beds due to reflection of waves, mean arterial pressure measured in the finger is likely to be proportional to the mean pressure measured in the MCA (23). If we also assume that intracranial pressure is low and relatively constant in healthy subjects, changes in the mean finger arterial pressure should therefore represent the changes in the cerebral perfusion pressure.

Bed-rest effects on CBF velocity. Spaceflight or ground-based simulations such as HDT bed rest remove or minimize hydrostatic gradients and cause a cephalad fluid shift (5, 30). These changes not only induce acute and adaptive hemodynamic responses by the systemic circulation, they also influence cerebral perfusion pressure and CBF (30). With acute exposure to HDT bed rest, cerebral blood velocity appears to increase with an increased intracranial arterial pressure (10, 17). However, after hours to days, velocity is indistinguishable from preflight measurements (3). When cerebral hemodynamics are assessed by a "resistance index," one study has shown a decrease in resistance during LBNP, and this change appeared not to be influenced by HDT bed rest (28). The authors argued that reduction in resistance may indicate efficient autoregulation to maintain blood flow during orthostatic stress. However, there are numerous problems with estimating resis-
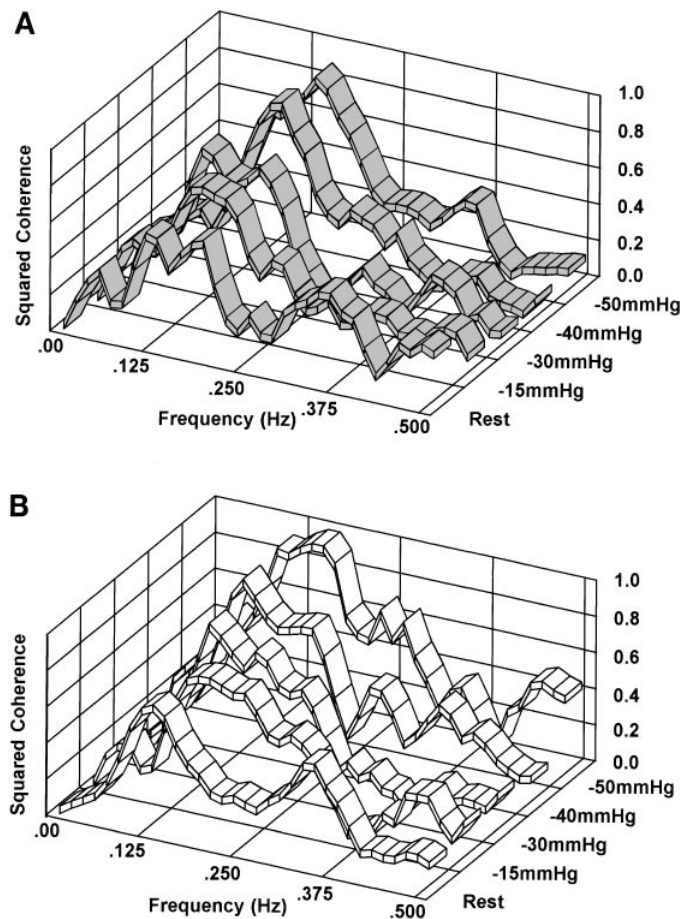
A

B

Fig. 4. Representative pre- (*A*) and post-bed-rest (*B*) magnitude-squared coherence function between beat-to-beat mean arterial pressure and cerebral blood flow velocity variability from 1 subject.

manifested by a significant increase in heart rate and both systemic and forearm vascular resistance. In a similar comparison involving the present study, in subjects after bed rest we observed a greater fall in stroke volume and greater increase in systemic and forearm vascular resistance during LBNP compared with before bed rest (Table 1). Therefore, we speculate that sympathetic activation may be more potentiated during orthostatic stress after bed rest. Although the augmented sympathetic activity is crucial for maintaining systemic blood pressure, it may eventually lead to cerebral vasoconstriction and a decrease in CBF velocity, and, presumably, flow. This outcome, although not likely to be a principal cause of syncope during orthostatic stress in the absence of systemic hypotension (19, 21), may predispose subjects to hypotension-induced syncope and partially contribute to the reduced orthostatic tolerance after bed rest.

Bed-rest effects on dynamic autoregulation. We previously hypothesized that, if the cerebral autoregulatory curve shifts rightward during high levels of LBNP due to increased sympathetic activity, the operating point of perfusion pressure and flow may fall below the lower limit range of the autoregulatory curve even without a significant change in mean arterial pressure (19). In this situation, changes in CBF velocity, and, presumably, flow, may become more dependent on the changes in pressure and the coherence between these two variables should be increased. In this study, the low-frequency coherence indexes (0.05–0.15 Hz) increased significantly at high levels of LBNP before bed rest and occurred earlier at −30 mmHg LBNP after bed rest. These changes may indicate an impairment of dynamic autoregulation during orthostatic stress.
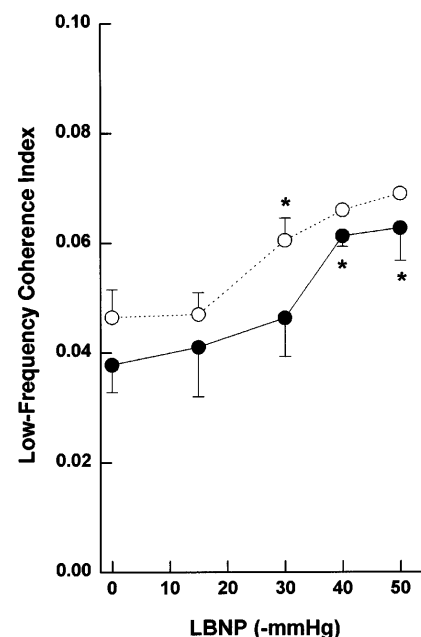
tance from an indirect index. Like other pulsatility indexes estimated from the velocity waveform, the resistance index (systolic − diastolic/systolic velocity) is importantly influenced by the systemic pressure pulsatility. A preponderance of the evidence suggests that CBF velocity decreases during orthostatic stress and is associated with cerebral vasoconstriction and an increase in vascular resistance (6, 14, 19).

In the present study, we observed no significant change in mean velocity at low levels of LBNP. However, with high levels of LBNP, mean velocity decreased and the corrected pulsatility ratio increased significantly without a significant change of mean arterial pressure. These results further confirmed previous findings from this laboratory and findings by others (6, 19). The present study extends these previous observations by demonstrating that velocity fell earlier at lower levels of LBNP and that the decrease was greater after 2 wk of bed rest associated with a substantial reduction in orthostatic tolerance. In a previous study (19), we demonstrated that, in subjects who were prone to syncope during LBNP, the decease of velocity also occurred earlier at lower levels of LBNP compared with more resistant subjects. These changes occurred simultaneously with augmented sympathetic activity, as

Fig. 5. Time course of changes in low-frequency coherence index during progressive LBNP. Values are means ± SE. At post-bed-rest LBNP levels of −40 and −50 mmHg, *n* = 2. Symbols are defined as in Fig. 2. *$P < 0.05$ compared with rest.

In summary, we have demonstrated a more prominent decrease in CBF velocity during orthostatic stress after 2 wk of HDT bed rest, associated with a substantial reduction in orthostatic tolerance. These changes occurred simultaneously with a significant increase in coherence between beat-to-beat mean arterial pressure and CBF velocity, which suggests an impairment of cerebral autoregulation. Consequently, this impairment of autoregulation may contribute to the reduced orthostatic tolerance after adaptation to simulated microgravity.

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